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ABSTRACT

The goal of this training program is to dramatically extend our existing, highly successful Interdicsiplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates new faculty from the Lombardi Comprehensive Cancer Center Programs in Cancer Prevention and Control, and Cancer Genetics. The program is enriched by new courses, as well as practical research experience. This new programmatic initiative makes use of the existing organization structure of the Interdisciplinary Doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. To date, 12 students were recruited into 6 classes, and 4 new courses were created. Students in this program so far have published 20 papers, and 31 abstracts/presentations. They were also awarded 6 individual fellowship grants, and two have now been awarded the PhD, with others currently in the program continuing to make good progress toward that goal.

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COMBINED MD/PHD TRAINING PROGRAM IN BREAST CANCER PREVENTION

INTRODUCTION

The goal of this program is to significantly extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates faculty from the Lombardi Comprehensive Cancer Center. To date, 6 MD/PhD and 6 PhD candidates were matriculated into this program. The program is enriched by new courses covering cancer genetics, molecular epidemiology, and cancer prevention, as well as practical research experience. To date, 4 new courses, including 2 electives and two core courses, have been developed. The new programmatic initiative makes use of the existing organization structure of the Interdisciplinary Doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. We have recently had approved an extension of this grant period from 6 years to 7 years, in order to optimize our recruitment of the best qualified candidates for the available budget and allow completion of available funds by students in the program.

BODY

Training and Research Accomplishments

The accomplishments of this program, now finishing its sixth year, fall into two categories: the recruitment and progress of trainees, and the development of courses for the program. In the sixth year, we recruited Ms. Anne Miermont and Mr. Mark Markowski. Ms. Miermont received her BS in Cell Biology from the Universite Francois Rabelais, and received an MS in Applied Molecular Biology from the University of Maryland, Baltimore County. Mr. Markowski, an MD/PhD student received his BS in Biochemistry and Mathematics from Georgetown University. Ms. Miermont is currently working in the lab of her Thesis Mentor, Dr. Priscilla Furth. Mr. Markowski is currently working in the lab of Thesis Mentor Dr. Edward Gelmann.

The fifth year brought us two additional recruits, Mr. Ogan Abaan and Ms. Maria Frech. Mr. Abaan received his BS and MS in Biology from the Middle East Technical University in Ankara, Turkey. Ms. Frech received her BS in Pharmacy from the Universidad Nacional de Rosar and has an MS in Food Technology from the Universidad Catolica Argentina; both Universities are in Rosario, Argentina. Mr Abaan has completed his Comprehensive Exam and is now doing research on PTPL1 in Ewing's Sarcoma Tumorigenesis. Ms. Frech is working on her thesis research with Dr. Furth, and has recently secured her own grant from the DOD towards her Breast Cancer Research.

In the fourth year, we recruited Mrs. Youhoung Wang to the program. Mrs. Wang joined the Tumor Biology program with advanced standing, as she has transferred from University of Illinois' Microbiology and Immunology PhD program and has a MS degree in Cellular and Molecular Biology from Sun Yat-sen University of Medical Sciences in China. Mrs. Wang completed her laboratory rotations, passed her Comprehensive Exams and is now in PhD research with Dr. Dickson studying Cell Survival mechanisms. Ms. Wang received a DOD predoctoral Fellowship to support her work.

Ion Cotarla, M.D. appointed during the third year of the program, has completed his comprehensive examination and is working on the regulation and function of Stat5 in normal and malignant mammary epithelial cells, in Dr. Priscilla Furth's laboratory. Dr. Cotarla received a DOD Predoctoral Fellowship grant to support his work. Riddhish Shah, M.D., also in the third year of the program, is continuing his thesis research project, TGF beta regulator region polymorphism and its functional significance, with Dr. Carolyn Hurley. Rita

Kralik, M.D., was also appointed into the third year of the grant, but elected to take an MS degree in Tumor Biology due to personal reasons.

Three trainees had been recruited for the second incoming class of the Program: one MD/PhD candidate, Ms. Carolyn Lee, and two PhD candidates, Ms. Sonia de Assis and Mr. Elijah Herbert. Ms. de Assis is in her fifth year of the program, she received a DOD predoctoral fellowship, and she is now working with her thesis mentor, Dr. Hilakivi-Clarke. Her thesis project concerns dietary factors during pregnancy and breast cancer. Ms. Lee completed her thesis research with Dr. Todd Waldman on breast cancer genetics and has just successfully defended her PhD thesis. She has returned to Medical School to complete the MD portion of her training. Unfortunately, Mr. Elijah Herbert withdrew from the program after only a few months for very acute health reasons; we were able to use his slot in the program for recruitment of Ms. Carolyn Lee (above).

Two trainees had been recruited into the first incoming class, Ms. Christine Coticchia and Ms. Stacey Kessler. Ms. Coticchia has received a DOD predoctoral fellowship, and is proceeding with thesis research with Dr. Robert Dickson, studying c- Myc mediated apoptosis in mammary carcinoma cells. Unfortunately, Ms. Kessler withdrew from the program for personal reasons, but she earned an MS degree in Tumor Biology. However, the funds made available due to her departure were productively used to recruit a student with advanced standing into the third class (Sonia de Assis, see above).

In addition to the existing core course work of our GU Interdisciplinary Doctoral Training Program in Tumor Biology, new course components have been incorporated into our Breast Cancer Prevention track since Spring, 2002. These include a course in Biostatistics, Applied Biostatistics, that has been refocused on statistical design and methodology for research rather than biostatistics theory, and a Cancer Genetics course, Genetics, Health, and Society in the 21st Century, which focuses on practical and ethical questions raised by genetic information and technology. Both courses have been very successful and continue to be offered. Applied Biostatistics has become a required course for Tumor Biology PhD and MS students. A new course in Genetics, Human and Microbial Genetics, had a successful first two years. Most recently, a Cancer Prevention and Epidemiology Course was created as a new core course.

All of these courses emphasize breast cancer, as most of the teaching faculty are extensively involved in breast cancer research. Interest in these courses has not been limited to students in the new Breast Cancer Prevention track: a number of additional students in the Interdisciplinary Doctoral Training Program in Tumor Biology and other biomedical graduate programs at Georgetown University have enrolled as well.

KEY RESEARCH ACCOMPLISHMENTS

• *Recruitment of New Trainees and Advancement of Existing Trainees:*

Class #6

- Mr. Mark Markowski began with a laboratory rotation with Dr. Priscilla Furth, and then moved into the lab of Dr. Edward Gelmann.
- Ms. Anne Miermont began with a laboratory rotations with Dr. Priscilla Furth and Dr. Carolyn Hurley. She has settled into her thesis research in the lab of Dr. Furth.

Class #5

- Ms. Maria Silvina Frech began with a laboratory rotation with Dr. Priscilla Furth, and then worked with Dr. Suzette Mueller. She has begun her PhD thesis work with Dr. Furth.
- Mr. Ogan Abaan has begun his PhD thesis work with Dr. Toretsky.

Class #4

- Mrs. Youhong Wang has begun her PhD thesis work with Dr. Dickson.

Class #3
- Riddhish Shah, M.D. completed in his thesis research with Dr. Hurley, and successfully defended his thesis.
- Ion Cotarla, M.D. continues his thesis research portion of the program. with Dr.Furth

Class # 2
- Ms. Carolyn Lee completed her thesis research with Dr. Waldman, successfully defended her thesis, and has re-entered GU Medical School this fall to complete her MD/PhD training.
- Ms. Sonia de Assis continues her thesis research with Dr. Hilakiv-Clarke.

Class # 1
- Ms. Christine Coticchia is in the final year of her thesis research with Dr. Dickson. She is expected to defend her thesis in 2005.

REPORTABLE OUTCOMES

• *Student Publications:*

- **Abaan, O.** Levenson, A., Khan, O., Furth, P., Uren, A., and Toretsky, J.A. PTPL1 is a Direct Transcription Target of EWS-FLI1 and Modulates Ewing's Sarcoma Tumorigenesis. Oncogene 24(16): 2715-2722, 2005.

- **Lee, C.**, Kim, J.S., and Waldman, T. PTEN Gene Targeting Reveals a Radiation-Induced Size Checkpoint in Human Cancer Cells. Cancer Research 64(19): 6906-6914, 2004.

- Kim, J.S., **Lee, C.**, Foxworth, A., and Waldman, T. B-Raf is Dispensable for K-Ras-Mediated Oncogenesis in Human Cancer Cells. Cancer Res 64(6): 1932-1937, 2004.

- Hilakivi-Clarke, L. Cabanes, A., **de Assis, S.**, Wang, Md., Khan, G., Shoemaker, W.J., and Stevens, R.G. In Utero Alcohol Exposure Increases Mammary Tumorigenesis in Rats. Br J Cancer 90(11): 225-2231, 2004.

- Cabanes, A., Wang, M., Olivo, S., **de Assis, S.**, Gustafsson, J.A., Kahn, G., and Hilakivi-Clarke, L. Prepubertal Estradiol and Genistein Exposure Up-Regulate BRCA1 mRNA and Reduce Mammary Tumorigenesis. Carcinogenesis 25(5): 741-748, 2004.

- **Frech, M.S.**, Halama, E.D., Tilli, M.T., Singh, B., Gunther, E.J., Chodosh, L.A., Flaws, J.A., Furth, P.A. Deregulated Estrogen Receptor α Expression in Mammary Epithelial Cells of Transgenic Mice Results in the Development of Ductal Carcinoma in Situ. Cancer Research, 2005 Feb 1; 65(3): 681-5.

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- **Cotarla I.** PI 3-kinase superfamily and breast cancer. Radiotherapy & Medical Oncology (2004); 10(1):3-27.

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- Kimura K, **Markowski M,** Edsall LC, Spiegel S, Gelmann EP, Role of ceramide in mediating apoptosis of irradiated LNCaP prostate cancer cells, Cell Death Differentiation, 10(2): 240-248, 2003.

- Ramljak D, **Coticchia CM**, Nishanian TG, Saji M, Ringel MD, Conzen SD, and Dickson RB. Epidermal Growth Factor Inhibition of c-Myc-mediated Apoptosis Through Akt and Erk involves Bcl-xL upregulation in mammary epithelial cells, Experimental Cell Research, 287:397-410, 2003

- Cavalli LR, Urban CA, Dai D, **De Assis S**, Tavares DC, Rone JD, Bleggi- Torres LF, Lima RS, Cavalli IJ, Issa J-PJ, and Haddad BR. Genetic and Epigenetic Alterations in Sentinel Lymph Nodes Metastatic Lesions Compared to Their Corresponding Primary Breast Tumors. Cancer Genet Cytogenet 145:1-8, 2003.

- Waldman T, **Lee C**, Nishanian TG, and KiM JS. Human Somatic Cells Gene Targeting. In: Ausubel, FM, Brent R, Kingston, RE, Moore D, Seidman J, Smith J, Struhl K, editors. Current Protocols in Molecular Biol. ("The Red Book"). New Jersey: John, Inc.; p. 9.15.1-p. 15.20, 2003.

- **Lee C**, and Waldman T. Human Somatic Cell Knockouts Reveal Determinants of Sensitivity and Resistance to Proteasome Inhibitor PS-341. Cancer Biology and Therapy, 2: 700-701, 2003.

- Hruska KS, Tilli MT, Ren S, **Cotarla I**, Kwong T, Li M, Fondell JD, Hewitt JA, Koos RD, Furth PA, and Flaws JA. Conditional Over-Expression of Estrogen Receptor Alpha in a Transgenic Mouse Model. Transgenic Research 11: 361-372, 2002.

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- Hilakivi-Clarke L, Cho E, Cabanes A, **de Assis S**, Olivo S, Helferich W, Lippman ME, and Clarke R. Dietary Modulation of Pregnancy Estrogen Levels and Breast Cancer Risk Among Female Rat Offspring. Clin Cancer Res 8: 3601-3610, 2002.

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- Kimmura K, **Markowski M**, Bowen C, Gelmann EP, Androgen blocks apoptosis of hormone-dependent prostate cancer cells, Cancer Res 61(14): 5611-568, 2001.

• *Student Abstracts/Presentations:*

- **Wang Y**, Deb T, and Dickson R, Towards identification of human p55pik-interacting proteins: production and characterization of p55plk recombinant proteins and antibodies, DOD ERA of Hope Meeting, Philadelphia, PA, 2005.

- Kim, J.S., Bonifant, C.L., **Lee, C.**, and Waldman, T. B-Raf Is Dispenssable for K-Ras Mediated Oncogenesis in Human Cancer Cells. Cancer Genetics and Tumor Suppressor Genes. Cold Spring Harbor Laboratory, NY, 2005.

- Effects of Overexpression of ERα on Female Reproduction. Tomic, D., Babus, J., **Frech, M.S.**, Furth, P.A., Koos, R.D., Flaws, J.A. Endocrine Society Meeting, 2005.

- Tilli, M.T., Parrish, A.R., Halama, E.D., **Frech, M.S.**, Riegel, A.T., Furth, P.A. Overexpression of AIB1 Augments Progesterone Receptor Signaling ina Mouse Model of ERα-Initiated Preneoplasia and DCIS. American Society for Investigative Pathlology Annual Meeting; 2005.

- **Frech, M.S.**, Halama, E.D., Tilli, M.T., and Furth, P.A. A Conditional Transgenic Mouse Model of ERα Initiated Preneoplasia and Ductal Carcinoma in Situ for Preclinical Testing of Chemopreventive Agents. Third Annual AACR International Conference on Frontiers in Cancer Prevention Research; Seattle, Washington; October 16-20, 2004; #C38.

- **Cotarla I**, Johnson MD, Luo J, Cantley LC, Furth PA. Regulation of Cyclin D1 protein levels in the mammary gland by PI3K pathways. Biol Reprod (2004, Suppl.): A168.

- Furth PA, Tilli MT, **Cotarla I**, de Guzman JRV, Jones LP, Russell R, Freedman M. Ultrasonic Imaging of Normal, Preneoplastic, Malignant Mammary Gland and Metastatic Lesions in Mice. Molecular Imaging (2004, SI): A252.

- **Cotarla I**, Johnson MD, de Guzman JRV, Russell R, Freedman M, Furth PA. Ultrasonography - a powerful tool for monitoring mammary gland transplants, as well as mammary carcinoma development and progression in mice. Proceedings of the 96th American Association for Cancer Research Annual Meeting, Anaheim, CA; April 2005.

- **Cotarla I**, Luo J, Cantley LC, Johnson MD and Furth PA. Stat5a and PI3K pathways collaborate in maintaining Cyclin D1 protein levels in the mammary gland. Poster presentation finalist in the 6th Annual Lombardi Research Fair (February 9, 2004), Georgetown University 18th Annual Student Research Day (February 26, 2004), and Graduate Student Organization Research Fair (April 14, 2004), Washington, D.C.

- **Cotarla I**, Luo J, Cantley LC, Johnson MD and Furth PA. Stat5a and PI3K pathways collaborate in maintaining Cyclin D1 protein levels in mammary epithelial cells. FASEB's "Experimental Biology" Annual Meeting, Washington, DC (2004) – abstract selected for a platform presentation in the American Society for Investigative Pathology (ASIP) session "Highlights: Graduate student posters in pathology".

- **Cotarla I**, Luo J, Cantley LC, Johnson MD and Furth PA. Regulation of Cyclin D1 protein levels in the mammary gland by Stat5a and PI3K pathways. Selected for the final oral competition of the Society for Experimental Biology and Medicine, Washington D.C. Chapter graduate student research forum (May 2004).

- **Cotarla I**, Johnson MD, Luo J, Cantley LC, Furth PA. Regulation of Cyclin D1 protein levels in the mammary gland by PI3K pathways. Abstract selected for a platform presentation at the 37th Annual Meeting of the Society for the Study of Reproduction; Vancouver, BC, Canada (August 2004).

- **Frech MS**, Halana Ed, Jilli MT, Chodosh LA, Flaus JA, and Furth PA, Dysregulating expression of estrogen receptor in a mammary epithelial cells results in development abnormalities and ductal

hyperplasia. *American Society for Investigative Pathology Meeting*, Washington, DC, 2004

- **Shah R,** Hurley C, and Posch P, Differential binding of nuclear factors to the common TGFβ promoter region single nucleotide polymorphisms-509 C to T and -800 G to A and their potential significance, *2004 Experimental Biology (Annual FASEB meeting),* AAI division, Washington DC. *Oral and poster presentations* (Block Symposium: Cytokine regulation, polymorphisms and chromatin).

- **Shah R,** Hurley C, and Posch P, Identification and characterization of transforming growth factor β promoter alleles, *2004 6th Annual Lombardi Science Research Fair – Student Division* – First Prize.

- **Shah R,** Polymorphisms in the extended 5' region and signal sequence of human TGFβ and its functional importance, *2004 GUMC Student Research Fair.*

- **Shah R,** Characterization of differential nuclear factor binding to common SNPs in transforming growth factor β_1 and its functional significance, *2004 GUMC Graduate Student Research Fair.*

- **Abaan OD**, Levenson A, Uren A, and Toretsky JA, The protein tyrosine phosphatase PTPL1 modulates ewing's sarcoma tumorigenesis. *95th Annual American Association for Cancer Research (AACR) Meeting,* Orlando, Fl, 2004.

- **Abaan OD**, Levenson A, Khan O, Furth PA, Uren A, Toretsky JA, The protein tyrosine phosphatase PTPL1 is a direct transcriptional target of EWS/FLI1 and modulates ewing's sarcoma tumorigenesis. *Lombardi Research Fair,* Washington, DC 2004.

- **de Assis S**, Cabanes A, and Hilakivi-Clarke L. Alcohol intake during pregnancy reverses the pregnancy-induced increase in p53 expression in the rat mammary gland. *American Association for Cancer Research,* Washington, DC 2003.

- **Cotarla I**, and Furth PA. Critical interactions between activated Stat5a and PI3K/Akt signaling pathways in normal and malignant mammary epithelial cells. *American Association of Cancer Research,* Washington, DC 2003.

- **Cotarla I**, Ren S, Li M, Zhang Y, Ghehan E, Singh B and Furth PA. Stat5 is activated in human breast cancers and associates with the p85 subunit of PI-3 kinase. Poster. Georgetown University Department of Medicine Research Day, Washington, DC; April 4, 2002. *Graduate Student Organization Research Day*; April 16-17, 2002. Meeting Abstract. *Proc Soc Exp Biol Med*, Washington D.C. Chapter Graduate Student Research Forum, Washington, D.C.; April 2002.

- **Cotarla I**, Ren S, Li M, Khan GA, Hilakivi-Clarke LA and Furth PA. Regulation and function of activated Stat5 in normal and malignant mammary epithelial cells. Poster 4th Annual Lombardi Research Fair, Washington, DC; February 19, 2002; *Georgetown University 16th Annual Student Research Day*, Washington, DC; February 21, 2002.

- **de Assis, S**, Ambrosone, CB, Wustrack, S, Krishnan, S, Frudenheim, JL, Shields, PG. Microsomal epoxide hydrolase polymorphisms and tobacco smoking in relation to risk of breast cancer. *American Association for Cancer Research*, San Francisco, CA, 2002.

- **de Assis S**, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.

- **de Assis S,** and Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. *4th Annual Lombardi Research Fair*. Georgetown University Medical Center, Washington, D.C. 2002.

- **Coticchia CM**, and Dickson RB. The role of c-Myc overexpression in sensitization of mammary epithelial cells to apoptosis. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.

- Ramljak D, **Coticchia CM**, Nishanian TG, and Dickson RB. AKT inhibits c-Myc-mediated apoptosis in mammary epithelial cells: a mechanistic investigation. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.

- **Coticchia CM**, Wang J-K, Dickson RB. Evaluation of pathways involved in CMyc-induced apoptosis of mouse mammary carcinoma cells. *4th Annual Lombardi Research Fair*. Georgetown University Medical Center, Washington, D.C. 2002.

- **Lee C,** Waldman T. Functional Analysis of PTEN in Human Cancer Cells by Human Somatic Cell Gene Targeting. *4th Annual Lombardi Research Fair*. Georgetown University Medical Center, Washington, D.C. 2002

- Selaru FM, Xu Y, Yin J, Shustova V, Zou T, Twigg C, Abraham JM, Mori Y, Sato F, **Cotarla I,** Greenwald BD and Meltzer SJ. Microarray and bioinformatics analyses discriminate among biologic subtypes of esophageal neoplasia. Meeting Abstract. *Gastroenterology*, 120 (5): 226, Suppl. 1, April 2001.

• *Predoctoral Fellowship Awards:*

- **Ann Miermont** just received a DOD Breast Cancer Research Program Predoctoral Traineeship award (effective July 15, 2005) to study Stat 5a in mammary ductal hyuperplasia and DCIS.

- **Maria Frech** received a DOD Breast Cancer Research Program Predoctoral Traineeship Award and an ACR Minority Scholar in Training Award in late 2004.

- **Christine Coticchia** received a DOD Fellowship Award in 2001 - Fas/Fas L System on c-Myc Expressing Mammary Carcinoma Cells.

- **Ion Cotarla** received a DOD Fellowship Award in 2003 – Nucleocytoplasmic Export of Stat5 in Normal and Malignant Mammary Epithelial Cells: Regulation and Implications in Breast Cancer.

- **Sonia de Assis** received a DOD Fellowship Award in 2003 – Pregnancy Leptin Levels and Breast Cancer Risk.

- **Youhong Wang** received a DOD Fellowship Award in 2004 – Transcription factor stat5 in invasion and metastasis of human breast cancer.

• *Thesis Defense:*

- **Carolyn Lee** successfully defended in 2004 her PhD thesis entitled: "Genetic Analysis of PTEN Function in Human Cancer Cells"

- **Riddhish Shah** successfully defended in 2005 his PhD thesis entitled:" Identification of an Extended

TGF-Beta1 Regulatory Region: Characterization of Regulatory Region Allelic Diversity and Functional Analyses of Novel and Known SNPs ".

CONCLUSIONS

The goal of our program was to extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. We have successfully recruits 12 students into 6 classes, and 4 new courses were created. Students have exhibited extraordinary creativity and productivity; 6 have been awarded individual fellowship grants. Two students were awarded the PhD, which others remaining in the program are making good progress toward that goal.